REMARKS

Reconsideration of this application is requested.

The non-elected claims have been canceled without prejudice to divisional filing thereon.

Claim 1 has been amended to stress unique aspects of the applicants' invention.

A minor change has also been made in claim 9 in view of the changes in claim 1 and new claim 27 has been added for consideration. Basis for new claim 27 is found at, for example, page 7, 2nd full ¶.

The amendment to claim 1 finds support at, for example, page 4, beginning in the last full ¶ and extending over through page 6, 2nd full ¶ of the applicants' disclosure.

The changes in claims 1 and 9 are highlighted in the Appendix attached hereto.

As will be evident, the amendment to claim 1 specifies that the tagging with a greater or lesser amount of fluorescence activity is due to the respective presence or absence in the tagged molecule, relative to the untagged molecule, of a fluorescent amino acid residue or a synthetic amino acid derivative as specified in the amino acid backbone of the polypeptide. It is submitted that the applicants' invention as defined, particularly with the amendment of claim 1, is fully enabled by the applicants' disclosure and otherwise appropriately claimed.

The Examiner is requested to reconsider the Section 112, 1st ¶ rejection of claims 1-12. The specification is believed to be fully enabling for the applicants' claims. Clearly, those skilled in the art are enabled to practice the invention in the

scope claimed without undue experimentation. The guidance and direction given in the applicants' disclosure, including the examples thereof, considered with the skill of the ordinary worker in the art, are more than adequate to enable the full use of the invention.

In rejecting the claims, the Examiner states that the quantity of experimentation needed is great "with little, if any, reasonable expectation of success" (page 3, 1st full ¶ of the action). The Examiner has not provided any evidence whatsoever to support this assertion and, to the contrary, the applicants believe that a person skilled in the art would in fact have a very reasonable expectation of success by following the applicants' disclosure.

In connection with the above, it is noted that the generation of tagged molecules *per se* is routine for the person skilled in the art, given the state of the art and the benefit of the present disclosure. Thus, the use of techniques such as site-directed mutagenesis and PCR to produce mutated polypeptides is now entirely routine. In particular, the present specification at pages 12-13 provides guidance for those skilled in the art to select particular amino acid residues of polypeptides suitable for substitution.

Given this teaching and the common general knowledge of those skilled in the art, the applicants submit that it would be a straightforward matter to produce tagged molecules suitable for use in the method of the invention.

The Examiner states that examples provided in the specification are prophetic. However, without agreeing with the Examiner, it is noted that there is nothing *per se* wrong with prophetic examples. The level of detail given is perfectly sufficient to provide those skilled in the art with all the information required to prepare

the necessary tagged molecules and then use them in the claimed method. Thus, the specification identifies particular amino acid residues which are suitable for substitution in each of the exemplified polypeptides.

Similarly, methods for purification of polypeptides are entirely standard for those skilled in the art, and numerous such methods (as exemplified at page 8 of the specification) are known to those skilled in the art. While precise purification protocols may vary from polypeptide to polypeptide, the person skilled in the art would certainly be aware of this and adapt the purification protocol accordingly.

It is noted that the Examiner has not provided any documentary evidence to provide even a *prima facie* case to doubt the sufficiency of the disclosure of the present specification.

As for the Examiner's comments under the heading "The Nature of the Invention", it is noted that the invention relates to a method of detecting a polypeptide by analysis of fluorescence activity. As such, the claimed method does not relate directly to "matters of physiology and chemistry". In any event, the mutations envisaged in polypeptides for use in the claimed method involve conservative substitutions of a limited number of amino acid residues. As such, the changes sought to be introduced into the polypeptide are extremely minimal, other than in terms of the fluorescence activity. Accordingly, it is not considered that any inherent unpredictability attaches to the method of the claimed invention once the art is taught to do what the specification says to do.

It is acknowledged that the relative skill of those in the art is extremely high. However, contrary to the Examiner's view, the state of the prior art relating to the background of the invention is by no means undeveloped. In contrast, the

Examiner's attention is drawn to the following publications: Waldman et al (1987 Biochim. Biophys. Acta, 931:66-71; 1988 Biochim. Biophys. Res. Com., 150(2):752-759 and Corinne, 1991 Biochemistry, 30:1028-1036) incorporated tryptophan residues at the substrate binding site of lactate dehydrogenase in order to investigate confirmational and structural changes in the enzyme when bound to its substrate. These publications are mentioned at page 2 of the present specification. The properties of the resulting LDH mutants were studied by fluorescence analysis.

WO 94/10200 (again mentioned at page 2 of the specification) does not teach fluorescence analysis of hGH but does disclose detailed methods for the synthesis, purification and administration of mutant forms of growth hormone.

In addition, the Examiner's attention is drawn to the following publications:

Kilhoffer et al (Biochemistry, 31:8098-8106 (1992)) prepared a number of mutant forms of calmodulin, in each of which a single substitution was made in order to introduce an additional tryptophan residue by means of site-directed mutagenesis. The effects of removal of calcium from the surrounding medium were then studied by monitoring tryptophan-mediated fluorescence, in order to investigate the structural and confirmational changes in the molecule.

Ernst and Behnke (Biochim. Biophys. Acta, 1089:331-338 (1991)) prepared, by site-directed mutagenesis, a mutant form of porcine pancreatic colipase (CLP), in which a tyrosine residue was substituted with tryptophan. They subsequently used fluorescence studies to examine the role of the tryptophan residue in the binding site of CLP.

Trigo-Gonzalez et al (Biochemistry, 31:7009-7015 (1992)) prepared mutant forms of chicken troponin C by means of site-directed mutagenesis in which a

phenylalanine residue at position 29 and/or 105 was substituted with tryptophan. A number of methods, including fluorescence analysis, were then used to investigate the properties of the mutant forms of troponin C.

Thus, contrary to the Examiner's assertion, the prior art contains numerous examples of the preparation, purification and fluorescence analysis of fluorescently tagged polypeptides, which retain biological activity. In spite of this, however, no one had heretofore proposed that such methods could provide the basis for detecting the presence of an exogenously administered polypeptide in a sample from a mammalian subject. This is the essence of the applicants' invention which in the context of the applicants' disclosure and the knowledge and skill of the art is clearly enabling in the full scope claimed. In this regard, the Examiner will note that each of the publications mentioned above was available to the person skilled in the art at the priority date of the present application.

For all of the reasons given above, it is submitted that the applicants have satisfied enablement requirements, as interpreted by the authorities cited by the Examiner. Accordingly, it is urged that the Examiner's Section 112, 1st ¶ rejection should be withdrawn and the claims allowed.

Allowance is requested.

Respectfully submitted,

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APPENDIX

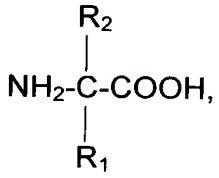
Version with Markings to Show Changes Made

IN THE CLAIMS

Claims 13-24 are being canceled.

The claims are amended as follows:

1. (Amended) A method of detecting the presence in a sample of a polypeptide exogenously administered to a mammalian subject from whom the sample is obtained, and distinguishing between such an exogenously administered polypeptide and a naturally-occurring endogenous polypeptide present in the sample; the method comprising obtaining a sample from the subject; and subjecting the sample to analysis of fluorescence at a suitable wavelength; wherein the exogenously administered polypeptide is tagged with a greater or lesser amount of fluorescence activity, relative to the untagged endogenous polypeptide, at the wavelength(s) analysed, wherein the greater or lesser amount of fluorescence activity is due to the respective presence or absence in the tagged molecule, relative to the untagged molecule, of a fluorescent amino acid residue or a synthetic amino acid derivative, in the amino acid backbone of the polypeptide, the synthetic amino acid derivative having the formula



wherein R_1 comprises the fluorophore and R_2 is H, OH, halide or substituted or unsubstituted lower alkyl.

9. (Twice Amended) A method according to claim 7, wherein the fluorophore comprises tyrosine or tryptophan[, or a synthetic amino acid derivative].

New claim 27 is being added.